

specification, for example, see page 32. Applicant submits that no new matter has been added.

Applicant gratefully acknowledges the courtesy extended by the Examiner in the telephonic interviews of January 30, 1997 and February 7, 1997.

The Examiner has objected to the disclosure in claims 28, 29 and 30, where a clerical error was made reciting "adminstering" instead of "administering". The error has been rectified by amendment, thereby obviating the objection.

Claims 9-13, 15-22 and 24-30 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner has rejected claims 9, 18, and 28-30 as non-enabling for "allelic variants". The Examiner states in the instant Office Action that there is no reasonable expectation of success and no working example of non-naturally occurring variants of TPO, such that fragments of the polypeptide or substitution, deletion or addition of a single amino acid residue within the polypeptide would enable a protein having biological activity.

Regarding the term "species homologs", the Examiner has alleged that the instant application does not demonstrate or provide adequate disclosure for TPO polypeptides from any species other than human or mouse.

Applicant respectfully traverses these grounds for rejection. Applicant believes that "allelic variant" is an art-accepted term originating with Gregor Mendel's observation that gene pairs segregate into gametes, each carrying one-half of the gene pair. Applicant is unaware of any work where "allelic variation" was used to describe anything other than naturally-occurring variations that arise from pairing of genes. Absent such knowledge, Applicant respectfully submits that the usual and art-recognized meaning of allelic variation would not result in innumerable variations encompassing any insertion, deletion or substitution, and thus, Applicant believes that the claims are not beyond the scope of the enabling disclosure.

However, because Applicant believes that elimination of the term "allelic variant" would expedite prosecution, Applicant has amended claims 9, 18, 28, 29, and 30 to recite: "A method of stimulating erythropoiesis comprising administering to a mammal in need thereof, a composition comprising a mammalian thrombopoietin protein of at least 323 amino acid residues selected from the group consisting of:

(a) a protein comprising the sequence of amino acids of SEQ ID NO: 4 from amino acid residue 45 to amino acid residue 379; and

(b) species homologs of (a)..."

As will be understood by those skilled in the art, natural variation would expected to exist in species homologs.

Support for thrombopoietin protein of at least 323 amino acid residues is found throughout the specification. For example, on page 12 the specification states that: "These changes are preferably of a minor nature, that is conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 2); small deletions, typically of one to about 30 amino acids...." The polypeptide described in SEQ ID NO: 4 is 353 amino acid residues in length. Deletion of 30 residues as described at page 12 yields a protein of 323 residues.

As for species homologs, Applicant has demonstrated that human TPO molecules are active in a mouse and therefore, predicted that other species homologs would show similar activity. Applicant submits that the Examiner has not met the burden of showing that such a prediction is not credible by presenting any evidence that repudiates Applicant's claim. The Examiner has cited a reference (The Cytokine FactsBook) that merely confirms the characteristics of murine and human TPO, as disclosed in the instant specification. The reference does not disclose that TPO is not active across other species lines. In

fact, the literature is replete with examples confirming that TPO activity crosses species barriers. For example, Bartley et al., Cell, 77:1117-1124, 1994; and Hunt et al., Blood, 86:540-547, 1995, demonstrated that canine TPO stimulated proliferation of human CD34⁺ positive cells; Li et al., Blood, 84 (10 Suppl. 1):330a, 1994, demonstrated that porcine and canine TPO stimulated proliferation of human CD34⁺ positive cells; and Kuter al., Blood, 84 (10 Suppl. 1):242a, 1994, demonstrated that ovine TPO increased platelet levels in rats. (Copies of these references are enclosed for the Examiner's convenience.) Applicant submits that the Examiner has failed to provide any specific information that would dispute Applicant's prediction that other TPO species homologs would stimulate proliferation or differentiation of myeloid or lymphoid progenitor cells. Thus, Applicant respectfully submits that the claims are fully enabled and requests the rejection be withdrawn and notice of allowance be given.

Claims 9, 18, 25, and 28-30 have been rejected under 35 U.S.C. § 112, second paragraph for failing to provide proper antecedent basis for "proteins" in sub-part (a).

Applicant has amended the claims to recite "protein" and thus, has obviated the rejection and respectfully requests it be withdrawn.

Claims 15 and 25 have been objected to as being dependent upon rejected base claims, and the Examiner indicates that they would be allowable if rewritten to incorporate all the limitations of the base claim and any intervening claims.

Applicant submits that amendments to the base claims and incorporation of the amendments in any dependent claims by virtue of their dependency obviates the objection and requests it be withdrawn.

On the basis of the above amendments and remarks, Applicant believes that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6672.

Respectfully Submitted,
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Enclosures:

PTO Form 1449
Petition and Supplemental Information Disclosure
Statement (in duplicate)
5 References
Notice of Appeal (in duplicate)
Postcard